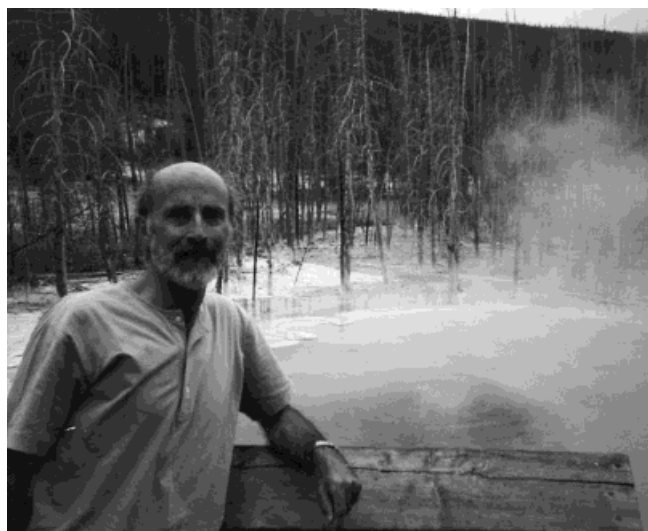


## *In Memoriam*

### Giorgio Filippi, April 4, 1935–January 19, 1996

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It is with gratitude and yet deep sadness that I accepted John Opitz's invitation to write an obituary for my closest collaborator and dearest friend, Giorgio Filippi, who died of cancer in his home at Trieste, Italy, last January 19 at the age of 61, tenderly cared for by his dear wife Fortunata and daughter Laura.

Giorgio graduated cum laude in medicine at the University of Rome in the late 1950s and specialized in pediatrics at the same university in the early 1960s. After a postdoctoral stage in Bruxelles, Belgium, where he was introduced to the biochemistry of human diseases, he won a tenured and well-paid position in the Italian National Health Service. However, before moving to the new assignment, he decided to respond to an advertisement circulated by the Genetics Department of the University of Rome (directed at the time by the late Prof. Giuseppe Montalenti, founder of the first institute of genetics in Italy and the beloved mentor of a large number of Italian geneticists, including Giorgio and myself) offering a modestly remunerated 3-year research contract to an established pediatrician prepared to participate actively in a NSF-sponsored research project on human population genetics in the island of Sardinia. In Montalenti's group, I had the responsibility

of coordinating these population studies, and it was my task to explain to the applicants the very demanding nature of the job. At the time I had already moved to the University of Leiden, and it was an urgent matter to place the Sardinian project in the right hands. For this reason, in the winter of 1963, I met with Giorgio repeatedly in Rome and in Sardinia to support him in his difficult decision to give up a secure future in the medical profession for what was no more than an attempt to enter the challenging, albeit at the time still obscure world of human genetic research.

Actually—he told me sometime after—what made him decide to accept the offer without hesitation was the attractive change of perspective that the new task implied: to go hunting for disease in populations rather than being called to the bedside of individual patients! He had evidently a built-in attraction to medical genetics. Thus it is no wonder that in 1967 he joined Victor McKusick for 2 years of advanced training in medical genetics at the Moore Clinic of the Johns Hopkins University Hospital, at the time the undisputed Mecca of the "trade." It was indeed there that Giorgio gained international recognition as medical genetist as witnessed by the large number of entries with his name in McKusick's catalog on "Human Inheritance in Man," which include the listing of a "Filippi syndrome."

After his return to Italy, he established himself in the Department of Genetics at the University of Cagliari, Sardinia, where he remained until 1973, first as senior scientist of the Italian National Research Council and then as Associate Professor of Genetics. His appointment to the chair of medical genetics at the University of Trieste in 1973 (a position he held at the time of his death) made no change in his lifelong habit of dedicating at least 2 months per year to our collaborative research program of human population genetics in Sardinia. This collaboration went on unabated for over 30 years until the very end of his life.

Giorgio's personal contribution to these studies was concentrated on the use of the G6PD polymorphism as a research tool in X-chromosome biology, such as X-inactivation mosaicism, X-chromosome nondisjunction, and on the linkage analysis between the G6PD locus and a large number of X-linked traits or diseases. It would be embarrassing for me, as group leader, to emphasize here the generally acknowledged significance of these studies, but I have no hesitation to state that none of the work done by our group in Sardinia on human population and medical genetics would have been

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possible without Giorgio's enthusiastic leadership and indefatigable drive. The secret of his success in handling these population and pedigree studies is that he was literally loved by his patients and their families for the care and respect he showed them during the data collection and throughout the years afterward.

When my own scientific interests diverted toward somatic cell genetics and molecular biology (after my move from Leiden to New York), my personal contribution to the Sardinian project suffered a standstill, and this led to the accumulation of incomplete research endeavors that Giorgio amiably called "the unfinished symphonies." When he called to give me the dreadful news of his fatal disease, he cheered me up with his ironic comment "now there is no way out, Marcello, we have to get together and finish at least some of those symphonies." Three of them were indeed finished and are now in press in the *American Journal of Medical Genetics*, one of the genetic journals Giorgio favored for its editorial policy of considering the reports of data on clinical semeiology as important as those on biochemical and molecular phenotyping.

At our last encounter, a week before the end, he was feeble in body but as strong as ever in mind and spirit. Our discussion had fallen again on the unfinished work; but—as I was leaving—he gave me a long meaningful handshake and said with a soft voice and his usual affectionate smile: "By the way, I never thanked you officially for having helped me to give up medicine for genetics, but you know that I never actually stopped from being primarily a physician. I consider myself lucky to have had such a happy life at home and at work. In particular I thank you for all you did to make me learn genetics." I smiled back, pretending the same peacefulness of mind but had to leave in a rush not to succumb to emotion. I very much regret now to have been unable to express to him "officially" my own and everybody's deep gratitude for the critical role he played to support the scientific achievements of the entire group but, especially, for the last unspoken lesson on courage and dignity that he taught us all throughout the long ordeal of his lost battle for life.

### LIST OF PUBLICATIONS OF GIORGIO FILIPPI

- Bottini E, Filippi G, Maggioni G (1962): Comportamento di alcune frazioni proteiche plasmatiche nel corso di anemia emolitica acuta da favismo nel bambino. (Studio elettroforetico su gel di amido). *Archiv It Ped* 22:368–374.
- Siniscalco M, Filippi G, Latte B (1964): Recombination between protan and deutan genes: data on their relative positions in respect to the G6PD locus. *Nature* 204:1062–1064.
- Siniscalco M, Filippi G, Latte B, Piomelli S, Rattazzi M, Gavin J, Sanger R, Race RR (1966): Failure to detect linkage between Xg and other X-borne loci in Sardinians. *Ann Hum Genet* 29:231–252.
- Siniscalco M, Bernini L, Filippi G, Latte B, Meera Khan P, Piomelli S, Rattazzi M (1966): Population genetics of hemoglobin variants, thalassemia and G6PD deficiency, with particular reference to the malaria hypothesis. *Bull World Health Org* 34:379–393.
- Bottini E, Filippi G, Cozzi F, Maggioni G (1966): A particular benzidine-positive protein fraction in the plasma of newborn and children with various haemolytic conditions. *Acta Haemat* 36:361–370.
- Bottini E, Filippi G, Cozzi F, Maggioni G (1966): Formation of a peculiar heme-protein fraction in plasmas containing hemoglobin. *Experientia* 22:19.
- Modiano G, Filippi G, Brunelli F, Frattaroli W, Siniscalco M (1966): Studies on red cell acid phosphatases in Sardinia and Rome: absence of correlation with past malaria morbidity. *Acta Genet Stat Med (Basel)* 17:17–28.
- Signoretti A, Filippi G, De Jong WW, Maggioni G (1966): Sindrome talassemica da interazione di Hb Lepore e beta-talassemia. *Riv Clin Pediatr* 78:721–729.
- Bottini E, Modiano G, Businco L, Filippi G (1967): Differential effect of oxydized glutathione or acetylphenylhydrazine on individual electrophoretic components of red cell acid phosphates. *Experientia* 23:107.
- Businco L, Spennati GF, Filippi G, Capotorti L, Bottini E (1967): Ricerche sul "principio tossico" della Vicia faba. *Minerva Pediatrica* 19:608–610.
- Modiano G, Scozzari R, Gigliani F, Filippi G, Latte B (1967): Studies on red cell phosphoglucomutase and adenylatokinase polymorphisms in Sardinia. *Rend Acc Naz Lincei, Cl Sc Fis Ser, VIII* 42:906–915.
- Filippi G, Macciotta A (1967): Xg blood-groups in muscular dystrophy. *Lancet* 2:565.
- Modiano G, Filippi G, Scozzari R, Gigliani F, Latte B, Siniscalco M (1968): Studies of genetical polymorphism of the red cells in Sardinia. Search for interaction at the individual and population levels. *Proc 9th Int Congr Life Ass Med Tel Aviv 1967, Karger, Basel*, 143–163.
- Modiano G, Filippi G, Brunelli F, Siniscalco M (1968): Red cell acid phosphate activity in carriers of  $\beta$ -thalassemia trait and glucose-6-phosphate dehydrogenase deficiency. *Isr J Med Sc* 4:858–866.
- Filippi G, Meera Khan P (1968): Linkage studies on X-linked ichthyosis in Sardinia. *Am J Human Genet* 20:564–569.
- Bottini E, Filippi G, Cozzi F, Maggioni G (1968): Remarks on the so-called "Hemoglobin Koelliker." Letter to the Editor of *Acta Haematologica* 39:60–61.
- Filippi G (1969): Case reports: A-1, the Rubinstein-Taybi Syndrome in a Negro. A-2, The Rubinstein Syndrome. *Birth Defects: Original Article Series, Vol. V, No. 2*:208–212.
- Filippi G, Renuart AW (1969): Case reports: K-2, Limb anomalies in the Cornelia de Lange Syndrome; Adult patient. *Birth Defects: Original Article Series, Vol. V, No. 3*:228–229.
- Lenzerini L, Meera Khan P, Filippi G, Rattazzi MC, Ray AK, Siniscalco M (1969): Characterization of glucose-6-phosphate dehydrogenase variants: I. Occurrence of a G6PD Seattle-like variant in Sardinia and its interaction with the G6PD Mediterranean variant. *Am J Hum Genet* 21:142–153.
- Carbonara AO, Trinchieri G, Bedarida G, Filippi G (1970): A Caucasian population with a high frequency of Au carriers: Genetic analysis of the condition. *Vox Sang* 19:288–294.
- Filippi G, McKusick VA (1970): The Beckwith-Wiedemann syndrome (The exomphalos-macroglossia-gigantism syndrome): Report of two cases and review of the literature. *Medicine* 49:279–298.
- Bottini E, Modiano G, Santolamazza C, Filippi G, Businco L (1970): Studies of the in vitro effects of oxydized glutathione and acetylphenylhydrazine on acid phosphatases of human red blood cells. An experimental model for the investigation of hemolytic drug action at the molecular level. *Clin Chim Acta* 31:243–254.
- Filippi G (1971): Hemifacial microsomia with vertebral anomalies: Case report. *Birth Defects: Original Article Series, Vol. VII, No. 1, February 1971*, 197–201.
- Filippi G (1971): Case reports: J-benign muscular dystrophy, Becker Type. *Birth Defects: Original Article Series, Vol. VII, No. 2, March 1971*, 110–112.
- Filippi G (1972): The syndrome of polydactyly, imperforate anus and vertebral anomalies. *Birth Defects: Original Article Series, Vol. VIII, No. 2, March 1972*, 88–94.
- Filippi G (1972): The Rubinstein-Taybi syndrome. Report of 7 cases. *Clin Genet* 3:303–318.
- Rinaldi A, Filippi G, Siniscalco M (1976): Variability of red cell phenotypes between and within individuals in an unbiased sample of 77 certain heterozygotes for G6PD deficiency in Sardinia. *Am J Hum Genet* 28:496–505.
- Romeo G, Rinaldi A, Urbano F, Filippi G (1976): Hair root versus red cell individual phenotype in Sardinian heterozygotes for G6PD deficiency (Mediterranean type). *Am J Hum Genet* 28:506–513.
- Filippi G, Rinaldi A, Palmarino R, Seravalli E, Siniscalco M (1977): Linkage disequilibrium for two X-linked genes in Sardinia and its bearing on the statistical mapping of the human X-chromosome. *Genetics* 86:199–212.

- Salabe GB, Filippi G (1977): Anticorpi anti-tireoglobulina in pazienti con sindrome di Klinefelter e nei loro familiari. *Minerva Endocrinologica* 2:169-174.
- Archidiacono N, Rocchi M, De Vonderweid U, Filippi G (1978): T(9/22) with centric fission and NOR translocation leading to a case of pure 9p trisomy in the offspring. *Hum Genet* 40:325-331.
- Rinaldi A, Velivasakis M, Latte B, Filippi G, Siniscalco M (1978): Triplo-X constitution of mother explains apparent occurrence of two recombinants in sibship segregating at two closely X-linked loci (G6PD and Deutan). *Am J Hum Genet* 30:339-345.
- Rocchi M, Stormi M, Archidiacono N, Filippi G (1979): Extra small metacentric chromosome identified as i(18p). *J Med Genet* 16:69-73.
- Filippi G, Rinaldi A, Crisponi G, Daniels G, Siniscalco M (1979): X-mapping in man: Evidence against measurable linkage between anhydrotic ectodermal dysplasia and G6PD deficiency. *J Med Genet* 16:223-224.
- Rinaldi A, Archidiacono N, Rocchi M, Filippi G (1979): Additional pedigree supporting the frequent origin of XYY from consecutive meiotic non-disjunction in paternal gametogenesis. *J Med Genet* 16:225-226.
- Archidiacono N, Tecilazich D, Tonini G, Rocchi M, Filippi G (1979): Trisomy 20 p from maternal t(3;20) translocation. *J Med Genet* 16:229-232.
- Archidiacono N, Rocchi M, Valente M, Filippi G (1979): X-pentasomy: a case and review. *Hum Genet* 52:69-77.
- Giammarini A, Rocchi M, Zennaro W, Filippi G (1980): XX male with breast cancer. *Clin Genet* 18:103-108.
- Lenzerini I, Benatti U, Morelli A, Pontremoli S, De Flora A, Piazza A, Rinaldi A, Filippi G, Siniscalco M (1981): Genetic variation in the quantitative levels of an NADP(H)-binding protein (FX) in human erythrocytes. *Blood* 57:209-217.
- Simoni G, Fraccaro M, Arslanian A, Bacchetta M, Baccichetti C, Bignone FA, Cagiano A, Carbonara AO, Carozzi F, Cuoco C, Dagna Bricarelli F, Dallapiccola B, Dalpra L, Doria Lamba Carbone L, Ferranti G, Filippi G, Frateschi M, Gimelli G, Gualtieri RM, Lenzi E, Micara G, Migone N, Montacuti V, Neri G, Papa R, Pecile V, Rocchi M, Savin E, Serra A, Tenconi R, Terzoli GL, Tibiletti MG (1982): Cytogenetic findings in 4952 prenatal diagnoses. An Italian collaborative study. *Hum Genet* 60:63-68.
- Siniscalco M, Szabo P, Filippi G, Rinaldi A (1982): Combination of old and new strategies for the molecular mapping of the human X-chromosome. In Bonne-Tamir B (ed): "Human Genetics, Part A: The Unfolding Genome." Alan R Liss, New York, pp 103-124.
- Filippi G, Rinaldi A, Archidiacono N, Rocchi M, Balazs I, Siniscalco M (1983): Brief report: Linkage between G6PD and fragile X-syndrome. *Am J Med Genet* 15:113-119.
- Filippi G, Pecile V, Archidiacono N, Baragino E, Auber G, Rocchi M (1983): X-chromosome replication patterns in a case of X;9 balanced translocation. *J Med Genet* 20:467-468.
- Purrello M, Nussbaum R, Rinaldi A, Filippi G, Traccis S, Latte B, Siniscalco M (1984): Old and new genetics help ordering loci at the telomere of the human X-chromosome long arm. *Hum Genet* 65:295-299.
- Filippi G, Mannucci PM, Coppola R, Farris A, Rinaldi A, Siniscalco M (1984): Studies on hemophilia A in Sardinia bearing on the problems of multiple allelism, carrier detection and differential mutation rate in the two sexes. *Am J Hum Genet* 36:44-71.
- Szabo P, Purrello M, Rocchi M, Archidiacono N, Alhadeff B, Filippi G, Toniolo D, Martini G, Luzzatto L, Siniscalco M (1984): Cytological mapping of the human glucose-6-phosphate dehydrogenase gene distal to the fragile-X suggests a high rate of meiotic recombination across this site. *Proc Natl Acad Sci USA* 81:7855-7859.
- Rocchi M, Cigui I, Archidiacono N, Pecile V, Procelli G, Filippi G (1984): A young girl with ring(18) mosaicism: Cytogenetic studies and PEP A mapping. *Clin Genet* 26:156-160.
- Rocchi M, Pecile V, Archidiacono N, Monni G, Dumez Y, Filippi G (1985): Prenatal diagnosis of the fragile-X in male monozygotic twins: Discordant expression of the fragile site in amniocytes. *Prenat Diagn* 5:229-231.
- Roth E Jr, Rinaldi A, Fiori GM, Filippi G (1983): The laboratory use of butylnitrite for the production of methemoglobin. *Am J Hemat* 20:153-159.
- Filippi G (1985): Unusual facial appearance, microcephaly, growth and mental retardation and syndactyly: A new syndrome? *Am J Med Genet* 22:821-824.
- Webster C, Filippi G, Rinaldi A, Mastropaolo C, Tondi M, Siniscalco M, Blau HM (1986): Linkage analysis of Duchenne phenotype and G6PD isotype in myoblasts from doubly heterozygous carriers. In Emerson C, Fischman DA, Nadal-Ginard B, Siddigui MAG (eds): "Molecular Biology of Muscle Development." Alan R Liss, New York, pp 911-919.
- Webster C, Filippi G, Rinaldi A, Mastropaolo C, Tondi M, Siniscalco M, Blau HM (1986): The myoblast defect identified in Duchenne muscular dystrophy is not a primary expression of the DMD mutation: Clonal analysis of myoblasts from five double heterozygotes for two X-linked loci: DMD and G6PD. *Hum Genet* 74:74-80.
- Filippi G (1986): Klinefelter's syndrome in Sardinia. Clinical report of 265 hypogonadic males detected at the time of military check-up. *Clin Genet* 30:276-284.
- Rinaldi A, Purrello M, Filippi G, Siniscalco M (1986): G6PD as a tool and a target for studies on X-chromosome linkage. In Yoshida A, Beutler E (eds): "Glucose-6-Phosphate-Dehydrogenase." Academic Press, New York, pp 389-403.
- Purrello M, Alhadeff B, Shittington E, Buckton KE, Daniel A, Arnaud P, Rocchi M, Archidiacono N, Filippi G, Siniscalco M (1987): Comparison of cytologic and genetic distances between long arm subtelomeric markers of human autosome 14 suggests uneven distribution of crossing over. *Cytogenet Cell Genet* 44:32-40.
- Siniscalco M, Filippi G, Rinaldi A, Purrello M (1987): Molecular approach to diagnostic and preventive medicine. In Gallo R, Della Porta G, Albertini A (eds): "Monoclonals and DNA Probes in Diagnostic and Preventive Medicine." Raven Press, New York, pp 1-22.
- Rocchi M, Archidiacono N, Filippi G (1987): X-linked mental retardation: I. Martin-Bell syndrome (Report of 18 families). *J Genet Hum* 35:351-379.
- Archidiacono N, Rocchi M, Rinaldi A, Filippi G (1987): X-linked mental retardation: II. Renpenning syndrome and other types (Report of 14 families). *J Genet Hum* 35:381-398.
- Filippi G, Pecile V, Rinaldi A, Siniscalco M (1988): Fragile-X mutation and Klinefelter syndrome: a reappraisal. *Am J Med Genet* 30:99-107.
- Carothers AD, Filippi G (1988): Klinefelter's syndrome in Sardinia and Scotland: Comparative studies of parental age and other aetiological factors in 47,XXY. *Hum Genet* 81:71-75.
- Filippi G (1988): The de Lange syndrome: Report of 15 cases. *Clin Genet* 35:343-363.
- Pecile V, Petroni MG, Fertz MC, Filippi G (1990): Deficiency of distal 8p-: Report of two cases and review of the literature. *Clin Genet* 37:271-278.
- Rocchi M, Archidiacono N, Rinaldi A, Filippi G, Bartolucci G, Sanni C, Fancello C, Siniscalco M (1990): Mental retardation in heterozygotes fragile-X mutation: Evidence in favor of an X-inactivation-dependent effect. *Am J Hum Genet* 46:738-743.
- Mestroni L, Miani D, Di Lenarda A, Silvestri F, Bussani R, Filippi G, Camerini F (1990): Clinical and pathologic study of familial dilated cardiomyopathy. *Am J Cardiol* 65:1449-1453.
- Siniscalco M, Oberlé I, Melis P, Alhadeff B, Murray J, Filippi G, Mattioni T, Chen YT, Furneaux H, Old LJ, Posner JB (1991): Physical and genetic mapping of the CDR gene with particular reference to its position with respect to the FRAXA site. *Am J Med Genet* 38:357-362.
- Pecile V, Filippi G (1991): Screening for fra(X) mutation and Klinefelter syndrome in mental institutions. *Clin Genet* 39:189-193.
- Cianchetti C, Sannio-Fancello G, Fratta AL, Manconi F, Orano A, Pischedda MP, Pruna D, Spinici G, Archidiacono N, Filippi G (1991): Neuropsychological, psychiatric and physical manifestations in 149 members from 18 fragile-X families. *Am J Med Genet* 40:234-243.
- Filippi G, Arslanian A, Dagna-Bricarelli F, Pierluigi M, Grasso M, Rinaldi A, Rocchi M, Siniscalco M (1991): Premutation for the Martin-Bell syndrome analyzed in a large pedigree segregating also for G6PD deficiency: I. A working hypothesis on the nature of the FRAX mutations. *Am J Med Genet* 40:387-394.
- Cianchetti C, Filippi G, Sannio-Fancello G, Fratta AL, Marrosu MG, Dagna Bricarelli F, Siniscalco M (1992): Premutation for the Martin-Bell syndrome analyzed in a large Sardinian family: II. Neuropsychological and behavioral data. *Am J Med Genet* 43:103-110.

- Cianchetti C, Sannio-Fancello G, Fratta AL, Pischedda MP, Spinicci G, Marrosu MG, Filippi G (1992): Neuropsychological studies in families with fragile-X negative X-linked mental retardation. *Am J Med Genet* 43:505–509.
- Cristofori G, Filippi G (1992): Saethre-Chotzen syndrome with trigonocephaly. *Am J Med Genet* 44:611–614.
- Pierluigi M, Perfumo A, Giannotti A, Filippi G, Stagni L, Bargiacchi S, Dagna Bricarelli F (1993): Definizione del cariotipo in 610 famiglie con figlio Down. *Pathologica* 85 (Suppl.):61–62.
- Van Allen MI, Filippi G, Siegel-Bartelt J, Yong SL, McGillivray B, Zuker RM, Smith CR, Magee JF, Ritchie S, Toi A, Reynolds JF (1993): Clinical variability within Brachmann-de Lange syndrome: A proposed classification system. *Am J Med Genet* 47:947–958.
- Sherman SL, Maddalena A, Howard-Peebles PN, Brown WT, Nolin S, Jenkins F, Schwartz C, Tarrelton J, Shapiro LR, Smits APT, Van Oost BA, Youings S, Jacobs PA, Martinez F, Barnicoat A, Hockey A, Staley L, Hagerman R, Kennerknecht I, Steinbach P, Barbi G, Filippi G, Grasso M, Taylor SAM, Robinson H, Webb T, Broome D, Dixon J, Ferreira P, Gustavson KH, Meyer JL, Pai GS (1994): Characteristics of the transmission of the FMR1 gene from carrier females in a prospective sample of conceptuses. *Am J Med Genet* 51:503–506.
- Robledo R, Melis P, Schillinger E, Casciano I, Balazs I, Rinaldi A, Siniscalco M, Filippi G (1995): X-linked ichthyosis without STS deficiency. *Am J Med Genet* 59:143–148.
- Robledo R, Melis P, Marchi J, Laficara F, Rocchi M, Siniscalco M, Filippi G (1996): A +2.71 LOD score at zero recombination is not sufficient for establishing linkage between X-linked mental retardation and X-chromosome markers. *Am J Med Genet* 64:134–136.
- Robledo R, Melis P, Laficara F, Marchi J, Rinaldi A, Siniscalco M, Filippi G (1996): Further linkage evidence for the localization of mutational sites for nonsyndromic types of X-linked mental retardation at the pericentromeric region. *Am J Med Genet* 64:107–112.
- Grasso M, Perroni L, Dagna Bricarelli F, Rinaldi A, Robledo R, Siniscalco M, Filippi G (1996): Premutation for the Martin-Bell syndrome analyzed in a large Sardinian family: III. Molecular analysis with the StB12.3 probe. *Am J Med Genet* 64:283–286.